II. REMARKS:

A. Status of the Claims

Claims 1-9 were originally filed with the case. Claim 1 was amended in response to an Official Action mailed May 20, 2004. Claims 1-9 stand rejected in the present Action. Claims 1, 3, and 5-8 are amended herein. No claims are added herein. Claim 4 is canceled herein. Claims 1-3 and 5-9 remain pending.

B. The Claims are Definite

The Action rejects claims 1-9 under § 112, second paragraph as being indefinite for failing to particularly point out the subject matter of the invention. Specifically, the Action states that the recitation "3-benzoylphenylacetic acid or derivative of the formula" is confusing as to whether the derivative is limited to compounds having the recited formula. The Action further asserts that it is not clear in claim 3 why "3-benzoylphenylacetic acid" is recited. In light of the amendment to claim 1 to clarify that the recited formula represents derivatives of 3-benzoylphenylacetic acid" and the amendment to claims 3 to delete the recital of 3-benzoylphenylacetic acid, it is believed that the definiteness rejection is rendered moot. Therefore, Applicants respectfully request that the definiteness rejection be withdrawn.

C. The Claims are Patentable Over Kalgutkar

The Action rejects claim 1 as being anticipated by Kalgutkar (U.S. Patent No. 6,207,700). Kalgutkar is said to disclose the compounds included in the claimed formula are useful to treat angiogenesis-related disorders. Applicants respectfully traverse.

The present invention is directed to a method of treating an ophthalmic angiogenesis-related disorder by administering a therapeutically effective amount of 3-benzoylphenylacetic

acid, or a derivative thereof having the described formula. Kalgutkar discusses the use of certain secondary amides of certain NSAIDs to treat cancer. There is no discussion or suggestion within Kalgutkar to use the described secondary amides to treat ophthalmic angiogenesis-related disorders. Furthermore, the compounds recited in the currently pending claims are derivatives of the compounds disclosed in Kalgutkar, which the Examiner acknowledges on page 3 of the Action.

It is well settled that for a prior art reference to render a claim anticipated, that reference must set forth every element in the claim, either expressly or inherently. *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051 (Fed. Cir. 1987) (citing *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548, 220 U.S.P.Q. 193, 198 (Fed. Cir. 1983)). In other words, to support a rejection under section 102, a reference must show ***all*** features of the rejected claim(s). *Minnesota Mining & Mfg. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1569, 24 USPQ2d 1321 (Fed. Cir. 1992). The Federal Circuit has stated that "absence of a claim element from a prior art reference negates anticipation." *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 U.S.P.Q. 409 (Fed. Cir. 1984).

In light of the fact that the compounds recited in the pending claims as useful in the methods of present invention are different compounds from those recited in Kalgutkar (by the Action's own admission), and that Kalgutkar does not discuss the treatment of ophthalmic angiogenesis-related disorders, it is submitted that Kalgutkar cannot anticipate the claimed invention. Therefore, Applicants respectfully request that the anticipation rejection based on Kalgutkar be withdrawn.

D. The Claims are Patentable Over Bayly Or Kalgutkar in view of Hellberg

Next, the Action rejects all claims as being unpatentable over Bayly (U.S. Patent No. 5,994,379) or Kalgutkar in view of Hellberg (U.S. Patent 6,342,524). Bayly is said to disclose that diabetic retinopathy and tumor angiogenesis are cyclooxygenase-mediated proliferative disorders and to further disclose the recited routes of administration. Kalgutkar is said to disclose that COX-2 inhibitors are antiangioangenic and antitumorigenic. The Action acknowledges that the claimed invention differs over Bayly and Kalgutkar in reciting a compound that is a derivative of the compounds disclosed in Kalgutkar. Hellberg is said to disclose that the recited compounds are COX inhibitors and to further disclose ophthalmic administration. Applicants respectfully traverse.

Applicants reiterate previously stated arguments that Hellberg discusses the use of certain compounds to treat GLC1A glaucoma and does not discuss the treatment of angiogenesis-related disorders at all. Hellberg goes on beyond its first sentence to discuss the relationship of the GLC1A gene to the occurrence of glaucoma. The GLC1A gene encodes a 57 kD protein that is expressed in the trabecular meshwork (TM) (col. 2, lines 20-21). The expression of this protein is upregulated by glucocorticoids (col. 2, lines 23-25). The glucocorticoid induction of this TM protein has been suggested to be involved in the generation of glucocorticoid-induced ocular hypertension and glaucoma. (col. 2, lines 32-35). It is this effect, the increase in ocular hypertension caused by glucocorticoid induction of the GLC1A protein, that the '524 patent seeks to treat.

The '524 patent discusses the mechanism by which the glucocorticoid induction of the GLC1A protein causes an increase in ocular hypertension, or intraocular pressure (IOP). It states, in pertinent part:

> It is known that the trabecular meshwork cells have glucocorticoid receptors and that glucocorticoid binding with these receptors causes a change in trabecular meshwork cell gene expression. Known manifestations of this change include a reorganization of the cytoskeleton [ ] and increased deposition of the extracellular matrix material in trabecular meshwork cells. As a result, *the trabecular meshwork becomes "clogged" and unable to perform one of its most critical functions, that is, serving as a gateway for aqueous humor flow from the anterior chamber of the eye. When the aqueous humor flow out of the eye via the trabecular meshwork is diminished, the intraocular pressure of the eye rises.* If this state of elevated intraocular pressure (IOP) is maintained or frequently occurs, the optic nerve head can be damaged resulting in the loss of visual field.

(col. 3, lines 16-37, *citations omitted, emphasis added*). Hellberg's objective is to decrease the IOP in glaucoma patients suffering from an increased IOP due to glucocorticoid induction of the expression of the GLC1A. Hellberg does not discuss the administration of derivatives of 3-benzoylphenylacetic acid to treat angiogenesis-related disorders. In fact, Hellberg discusses the use of such compounds only in combination with a prostaglandin for the treatment of GLC1A glaucoma. Hellberg does not discuss the use of derivatives of 3-benzoylphenylacetic acid by themselves to treat angiogenesis-related disorders.

The purpose of the presence of non-steroidal cyclooxygenase inhibitors in the combinations of Hellberg is to prevent the expression of GLC1A and thereby prevent the development of ocular hypertension or increased IOP. (col. 5, lines 20-22). The prostaglandin in the compositions of Hellberg provides the "acute effect" for lowering IOP. The non-steroidal cyclooxygenase inhibitors, used in combination with the prostaglandins, are present to ameliorate the undesirable secondary side effects associated with prostaglandin therapy for the treatment of glaucoma, without significantly interfering with the desired IOP lowering. (col. 5, lines 28-35). Clearly, Hellberg's objective is to treat GLC1A glaucoma by lowering IOP, not to directly treat angiogenesis-related disorders. In fact, glaucoma is not considered an angiogenesis-related disorder.

It is well settled patent law that "obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art." *See In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992); MPEP § 2143.01.

Furthermore, the fact that a reference or references can be combined or modified is not sufficient to establish obviousness. For example, the Federal Circuit held in *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990), that the mere fact that combination or modification of a reference or references is possible does not establish obviousness of the resultant combination unless the prior art also suggests the desirability of the combination, *i.e.*, unless the prior art provides motivation to produce the resultant combination. *Mills*, 16 U.S.P.Q.2d at 1432; *see also* MPEP § 2143.01, page 2100-91.

The Action appears to be ignoring what Hellberg *fairly suggests* to one skilled in the art." *Bausch & Lomb*, 230 U.S.P.Q. at 419. As discussed above, Hellberg suggests to the skilled artisan that the administration of derivatives of 3-benzoylphenylacetic acid in combination with a prostaglandin will prevent the expression of GLC1A and thereby prevent the development of ocular hypertension or increased IOP. (col. 5, lines 20-22). The prostaglandin in the compositions of Hellberg provides the "acute effect" for lowering IOP. The non-steroidal cyclooxygenase inhibitors, used in combination with the prostaglandins, are present to ameliorate the undesirable secondary side effects associated with prostaglandin therapy for the treatment of glaucoma, without significantly interfering with the desired IOP lowering. (col. 5, lines 28-35). Clearly, Hellberg's objective is to treat GLC1A glaucoma by lowering IOP.

There is no suggestion or motivation within Hellberg to administer the compounds of the present invention by themselves for the sole purpose of treating angiogenesis-related disorders. As explained above, the focus of the invention of Hellberg is to lower IOP by administering a combination of compounds. The remainder of the description of the problem and the solution provided in Hellberg focuses on the increase of ocular hypertension caused by glucocorticoid induction of the GLC1A protein. This is what Hellberg seeks to treat.

Neither Bayly nor Kalgutkar discuss the compounds of the present invention at all, as acknowledged in the present Action. The references both appear to discuss COX-2 inhibition and its effects on angiogenesis, but neither mention amfenac, nepafenac or any ophthalmic angiogenic-related disorder other than corneal neovascularization. The present invention is the first to show that nepafenac and related compounds can be used to treat an ophthalmic angiogenesis-related disorder. Thus, Bayly and Kalgutkar cannot render the claimed invention obvious, either alone or in combination.

In light of the foregoing arguments, Applicants respectfully request that the rejected based on Hellberg in combination with Bayly or Kalgutkar be withdrawn.

E. The Double Patenting Rejections Will be Overcome with Terminal Disclaimers When Appropriate

Next, the Action provisionally rejects claims 1-9 under the judicially created doctrine of obviousness-type double patenting doctrine as being unpatentable over copending Application Nos. 10/344,881 and 10/417,466. The Action points out that these rejections are provisional, in that the copending applications have not yet been allowed. Applicants will file terminal disclaimers to overcome these provisional rejections upon a notice of allowability of the presently pending claims.

F. Conclusion

This is submitted to be a complete response to the outstanding Action. Based on the foregoing arguments, the claims are believed to be in condition for allowance; a notice of allowability is therefore respectfully requested.

The Examiner is invited to contact the undersigned attorney at (817) 551-4321 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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